Disease Progression in Adults With Hepatitis Delta Virus vs Hepatitis B Virus Monoinfection in Inpatient and Outpatient Settings in Italy

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Conclusions

- In Italy, patients with hepatitis delta virus (HDV) infection have an overall greater liver disease severity at baseline compared with patients with hepatitis B virus (HBV) monoinfection
- Moreover, patients with HDV have a significantly increased risk of progressing to greater liver disease severity compared with patients with HBV monoinfection
- These findings emphasise the need for earlier HDV diagnosis and targeted interventions to delay progression and reduce liver-related morbidity

Plain Language Summary

- Having both hepatitis B virus (HBV) and hepatitis delta virus (HDV) infection leads to a more severe form of viral hepatitis than having HBV infection alone
- This study compared disease progression between adults with both HBV and HDV infection and those with HBV infection alone in inpatient and outpatient settings in Italy
- Patients with both HBV and HDV infection were more likely to progress to a greater liver disease severity compared with patients with only HBV infection

Introduction

- Infection with HDV, a defective RNA virus that requires the presence of HBV for propagation, results in the most severe form of viral hepatitis and carries a greater risk of morbidity and mortality compared with HBV monoinfection[1-3]
- Compared with HBV monoinfection, HDV is associated with an increased risk of cirrhosis, hepatocellular carcinoma (HCC), liver transplantation (LT), and mortality[1-5]

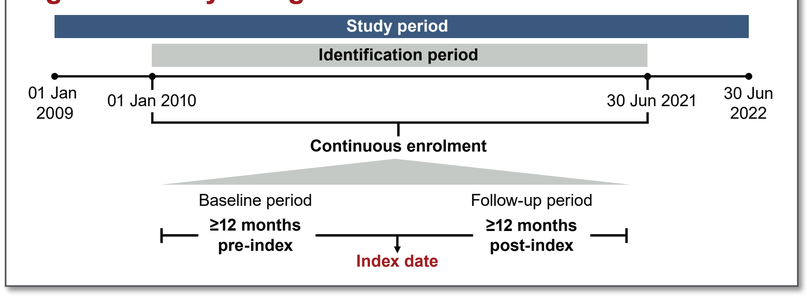
Objective

- To compare rates of disease progression between adults with HDV and those with HBV monoinfection in inpatient and outpatient settings in Italy

Methods

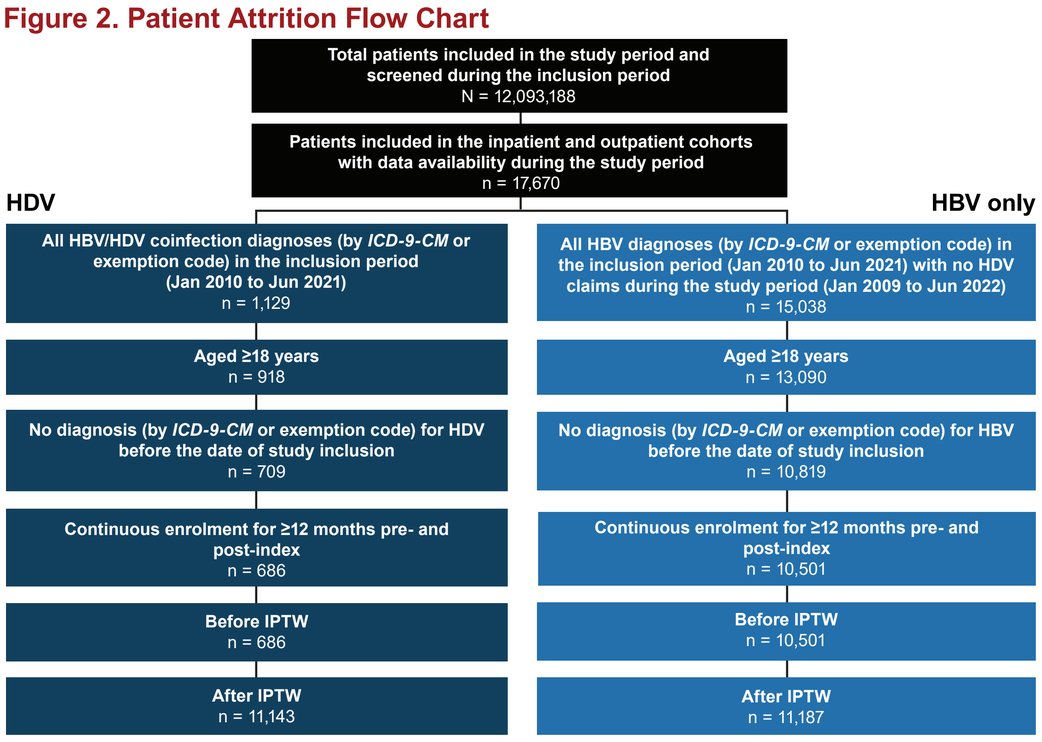
- In Italy, data from health care resources and services reimbursed by the National Health System are maintained in administrative databases from local health units covering approximately 12 million individuals
- **Study population and period:** adult patients (≥18 years of age) with ≥1 HBV or HDV hospitalisation discharge or diagnosis code via *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) between 1 Jan 2009 and 30 Jun 2022
- **Identification period**
  - HDV cohort: diagnosis with HDV infection between 1 Jan 2010 and 30 Jun 2021 via *ICD-9-CM* or exemption code
  - HBV-only cohort: diagnosis with HBV monoinfection between 1 Jan 2010 and 30 Jun 2021 via *ICD-9-CM* or exemption code
  - Incident patients were defined as patients without any diagnosis (*ICD-9-CM*) for HDV infection (HDV cohort) or HBV monoinfection (HBV-only cohort) before the date of inclusion in the study
- Propensity scores were generated for patients with HDV infection and HBV monoinfection based on baseline demographics and clinical characteristics assessed 12 months pre-index date
- Inverse probability of treatment weighting (IPTW), based on propensity scores, was used to adjust for measured confounders between patients in the HDV and HBV-only cohorts
- Fine and Gray's subdistribution hazard model was used to assess the risk of disease progression from any of the disease states to a higher-severity disease state, including LT, accounting for competing risks

Figure 1. Study Design and Patient Identification



Results

Figure 2. Patient Attrition Flow Chart



HBV, hepatitis B virus; HDV, hepatitis delta virus; *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification*; IPTW, inverse probability of treatment weighting.

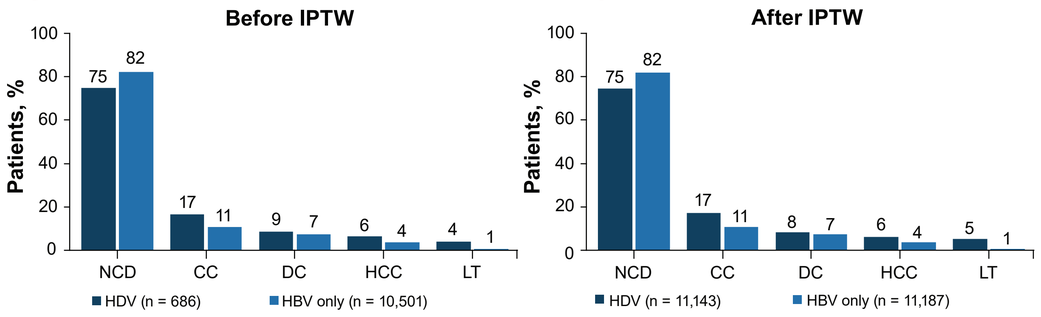
- Among 12,093,188 patients identified within the databases, 17,670 patients had data available
  - Of these, 11,187 were included in the analysis: 686 had HDV, and 10,501 had HBV monoinfection
  - After IPTW, 11,143 patients with HDV and 11,187 patients with HBV monoinfection were included in the analysis

Table 1. Demographics and Disease Characteristics at Baseline

	Before IPTW			After IPTW		
	HDV n = 686	HBV Only n = 10,501	*P*-Value	HDV n = 11,143	HBV Only n = 11,187	*P*-Value
Age, years, mean (SD)	54.8 (15.1)	55.9 (16.4)	.079	55.7 (16.2)	55.8 (16.4)	.845
Sex, male	446 (65)	6,588 (63)	.232	7,064 (63)	7,034 (63)	.423
QCCI, mean (SD)	1.1 (1.7)	1.1 (1.6)	.562	1.1 (1.7)	1.1 (1.6)	.871
Comorbidity profile						
STIs	<4 (NA)	48 (<1)	NA	54 (<1)	51 (<1)	.754
Hypertension	291 (42)	4,214 (40)	.236	4,502 (40)	4,506 (40)	.851
History of smoking	<4 (NA)	21 (<1)	NA	36 (<1)	23 (<1)	.087
HCV	167 (24)	712 (7)	**<.001**	893 (8)	880 (8)	.683
HIV	26 (4)	187 (2)	**<.001**	275 (3)	215 (2)	**.005**
Mental health disorder	104 (15)	1,580 (15)	.935	1,761 (16)	1,685 (15)	.125
Obesity	8 (1)	188 (2)	.227	165 (2)	197 (2)	.097
Substance abuse	13 (2)	152 (1)	.346	239 (2)	165 (1)	**<.001**
AAD/AUD	23 (3)	303 (3)	.481	535 (5)	329 (3)	**<.001**
NASH	14 (2)	274 (3)	.362	222 (2)	289 (3)	**.003**

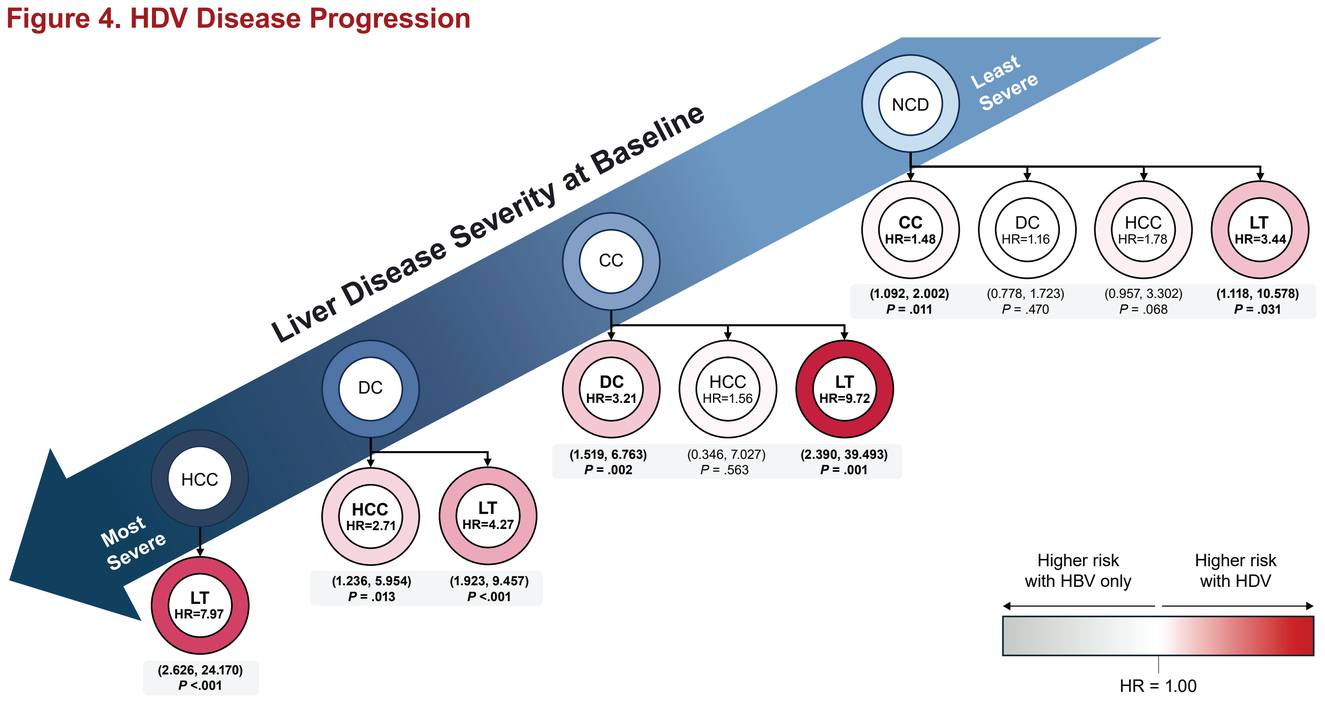
Data are reported as n (%) unless otherwise noted. **Bold** *P*-values indicate statistical significance.
AAD, alcohol abuse or dependence; AUD, alcohol use disorder; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis delta virus; IPTW, inverse probability of treatment weighting; NA, not applicable; NASH, nonalcoholic steatohepatitis; STI, sexually transmitted infection; QCCI, Quan-Charlson Comorbidity Index.

Figure 3. Differences in Liver Disease Severity at Baseline



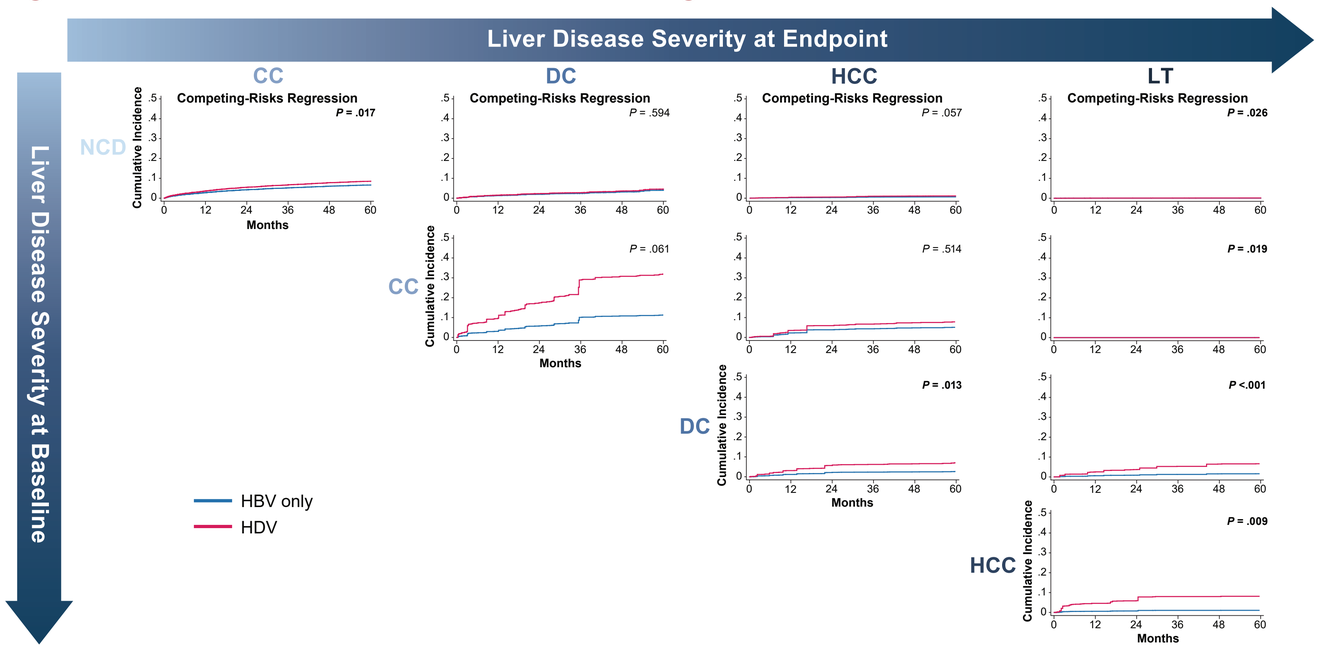
CC, compensated cirrhosis; DC, decompensated cirrhosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; IPTW, inverse probability of treatment weighting; LT, liver transplantation; NCD, noncirrhotic disease.

Figure 4. HDV Disease Progression



The numbers below the circles present 95% CIs. **Bold** values indicate statistical significance. Statistical significance was set at 0.05.
CC, compensated cirrhosis; DC, decompensated cirrhosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; HR, hazard ratio; LT, liver transplantation; NCD, noncirrhotic disease.

Figure 5. Cumulative Incidence of HDV Disease Progression



Bold *P*-values indicate statistical significance.
CC, compensated cirrhosis; DC, decompensated cirrhosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; LT, liver transplantation; NCD, noncirrhotic disease.

- Overall, patients with HDV were more likely than those with HBV monoinfection to progress to stages of greater disease severity
- Compared with patients with HBV monoinfection, those with HDV were more likely to progress from
  - Noncirrhotic disease (NCD) to compensated cirrhosis (CC) or LT
  - CC to decompensated cirrhosis (DC) or LT
  - DC to HCC or LT
  - HCC to LT

Limitations

- The limitations of any retrospective claims study apply. Diagnoses made via *ICD-9-CM* codes are subject to miscoding and can lead to misclassification bias, and time of diagnosis may not correspond to the time of infection
- This study may have underestimated the actual number of individuals with HDV infection due to a lack of approved diagnostic assays and suboptimal screening practices

References: **1.** Da BL, et al. *Gastroenterol Rep.* 2019;7:231-45. **2.** Gilman C, et al. *World J Gastroenterol.* 2019;25(32):4580-97. **3.** Miao Z, et al. *J Infect Dis.* 2020;221(10):1677-87. **4.** Muhammad H, et al. *World J Hepatol.* 2021;13(3):291-9. **5.** Muhammad H, et al. *J Liver Transpl.* 2021;4:100046.

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